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ANTICONVULSANT DRUGS (Classification and it's mechanism of action): A REVIEW

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Abstract:

Anticonvulsant drugs play a crucial role in managing a spectrum of neurological conditions beyond epilepsy. They work by stabilizing electrical activity in the brain through various mechanisms, such as blocking sodium and calcium channels, enhancing inhibitory neurotransmitter activity, and antagonizing excitatory neurotransmitter receptors. While effective in controlling seizures, anticonvulsants can cause side effects like drowsiness, dizziness, and gastrointestinal disturbances. Long-term use may lead to cognitive impairment and liver toxicity. These medications are also utilized in the treatment of neuropathic pain, bipolar disorder, and migraine prophylaxis. In neuropathic pain management, drugs like gabapentin and pregabalin are commonly prescribed due to their ability to modulate neuronal excitability and reduce pain signals. Additionally, certain anticonvulsants, such as valproate and carbamazepine, have mood-stabilizing properties and are used as adjunctive therapy for bipolar disorder. Furthermore, topiramate, another anticonvulsant, has demonstrated efficacy in preventing migraines and is often prescribed for migraine prophylaxis. Thus, anticonvulsant drugs contribute significantly to the therapeutic armamentarium for various neurological and psychiatric conditions beyond epilepsy.

Keywords: Epilepsy, Anticonvulsant drugs, mechanism of action, commonly used anticonvulsants.

INTRODUCTION

Epilepsy is a lasting neurological condition marked by repeated, unprovoked seizures. These seizures stem from abnormal electrical discharges in the brain, leading to alterations in consciousness, sensation, and behavior. A diagnosis of epilepsy typically occurs when the risk of spontaneous seizures is notably elevated, often observed after experiencing two such seizures[1]. Over recent decades, the introduction of numerous new antiepileptic medications has significantly expanded the options available for treating epilepsies[2].A restricted range of antiepileptic drugs (AEDs) have been available for treating patients with epilepsy. Until recently, the options were primarily limited to phenytoin (PHT), carbamazepine (CBZ), barbiturates and primidone (PRM),

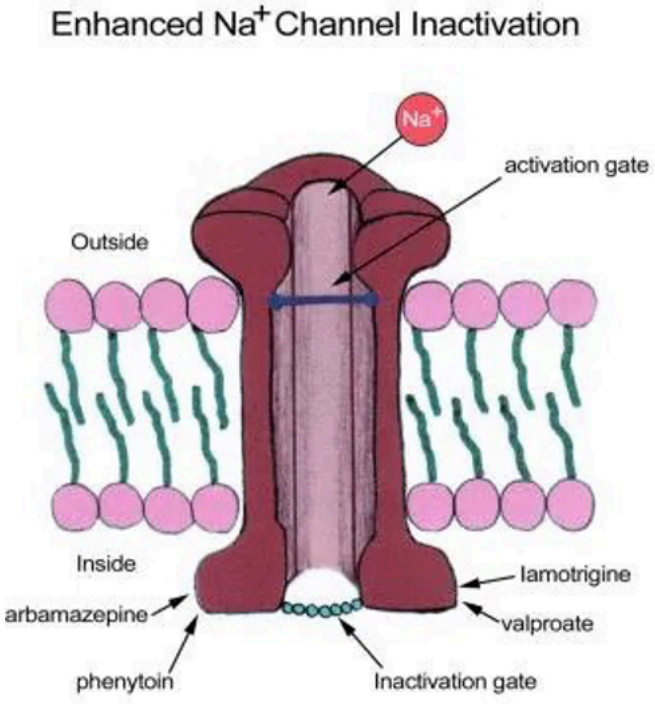
benzodiazepines (BZDs), valproate (VPA), and ethosuximide (ESM). However, in recent years, several new AEDs have become available. Among them, gabapentin (GBP), lamotrigine (LTG), oxcarbazepine (OCBZ), and vigabatrin (VGB) have emerged as promising additions to the treatment options[3].

MECHANISM OF ACTION OF ANTICONVULSANT DRUGS:

Numerous recently developed antiepileptic medications have been formulated to address seizure disorders. These established drugs work by decreasing neuronal excitability through mechanisms such as facilitating sodium channel inactivation, blocking T-type calcium channels, or augmenting inhibition mediated by gamma-aminobutyric acid type A receptors.[4] Medications prescribed for epilepsy are typically taken long-term to mitigate seizure occurrence. Generally, they modulate essential brain excitability mechanisms to dampen abnormal hyperexcitability and synchronized activity in brain circuits. Antiseizure drugs (ASDs) may not directly target the underlying pathogenic mechanisms of epilepsy, which are often poorly understood. However, recent advancements have identified molecular defects in numerous genetic epilepsies, sparking significant interest in developing targeted therapies specific to each disease[5].

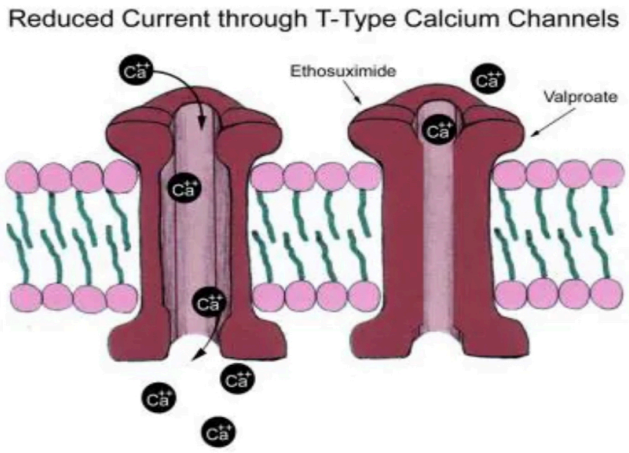
SODIUM CHANNEL BLOCKERS:-

Na+ channels - Voltage-gated ion channels in the nervous system oversee the movement of positively charged ions, including sodium, across cell membranes, both externally and internally.Among these channels, the sodium (Na+) channel is considered paramount. Voltage-dependent Na+ channels play a critical role in initiating the upstroke of neuronal action potentials, thereby exerting significant control over the intrinsic excitability of the nervous system[6].



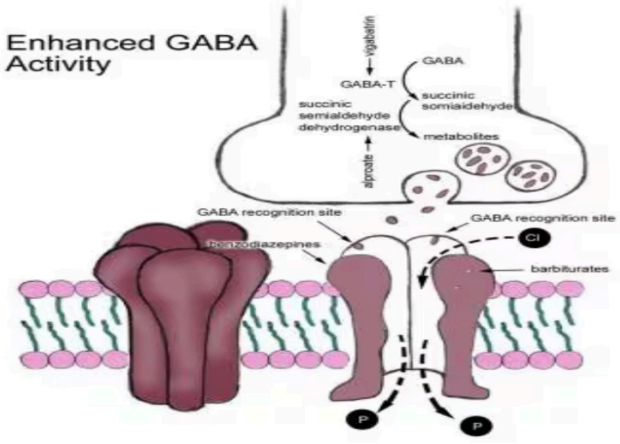
CALCIUM CHANNEL BLOCKERS:-

Alterations in the concentration of free calcium ions within cells serve as cues enabling nerve and muscle cells to react to various external triggers. One primary method for increasing intracellular calcium levels involves the entry of calcium from outside the cell through voltage-sensitive channels in the cell membrane. Recent studies have provided fresh understanding regarding the physiological characteristics, molecular composition, biochemical control, and diverse functions of voltage-sensitive calcium channels. Furthermore, drugs that block calcium channels have been created, serving as useful tools for investigating channel properties and as treatments for medical conditions[7].



GABA ENHANCERS:-

GABA operates through two receptor types: ionotropic and metabotropic. Ionotropic receptors include GABAa and GABAc, which are associated with chloride channels, while metabotropic receptors, like GABAb, trigger intracellular messenger cascades. The GABAa receptor complex, comprising various binding sites, responds to GABA, benzodiazepines, barbiturates, ethanol, and picrotoxin, a chloride channel blocker. GABA binding to GABAa receptors prompts chloride ion influx, leading to neuron hyperpolarization. GABAb receptor activation by GABA triggers phospholipase A-2 activity, leading to arachidonic acid synthesis from phospholipids. Arachidonic acid, regulated by Gi proteins, likely modulates adenyl cyclase activity and cyclic AMP levels, impacting neurotransmitter release crucial for neuronal function[8].



COMMONLY USED ANTICONVULSANTS:-

1. PHENYTOIN:- Phenytoin (also known as diphenylhydantoin or Dilantin) effectively treats partial and tonic-clonic seizures but is not effective against absence seizures. Its action occurs in the motor cortex, where it stabilizes neuronal membranes, preventing seizure spread. Current evidence indicates that it limits high-frequency repetitive firing by blocking sodium channels in a frequency-dependent manner. Additionally, it enhances calcium binding to neuronal membrane phospholipids, collectively resulting in a more stable membrane configuration.Phenytoin demonstrates antiseizure effects without inducing widespread CNS depression. However, in excessive doses, it can manifest excitatory symptoms, and at lethal levels, it may lead to a form of decerebrate rigidity[9].

2.BENZODIAZEPINES:- Diazepam (DZP) and midazolam (MDZ) are frequently employed in treating early (stage I) Status epilepticus. Midazolam, a water-soluble benzodiazepine, offers various administration routes: intravenous, intramuscular, buccal, and intranasal. In contrast, DZP can be given intravenously or rectally. Rectal DZP is commonly used for prehospital management of early SE in Spain and potentially elsewhere, although its administration is often socially unacceptable. Additionally, its use entails removing clothing and positioning the patient properly, which may cause significant treatment delays. Similar challenges exist with intravenous administration of DZP or other drugs like lorazepam, necessitating intravenous access placement[12]

3.ZONISAMIDE:- Zonisamide, a sulfonamide compound with chemical similarities to an indole, was identified for further development as an antiepileptic drug due to its effectiveness in maximal electroshock experiments. It is approved for use as both monotherapy and adjunctive therapy for partial onset and generalized epilepsies in Japan and South Korea, and for partial onset epilepsy in Europe. Zonisamide exhibits broad-spectrum antiepileptic properties with various mechanisms of action, including reducing sustained high-frequency repetitive firing of sodium-dependent action potentials, inhibiting low threshold T-type calcium currents, modulating GABA-mediated neuronal inhibition, inhibiting glutamate release, and weakly inhibiting carbonic anhydrase[13].

4.CENOBAMATE:- Cenobamate, an antiseizure medication prescribed for partial-onset (focal) seizures, is characterized by a single chiral center. It operates through a distinctive dual mechanism: enhancing both fast and slow inactivation of sodium channels, with a preference for inhibiting persistent current, and positively modulating GABAA receptor-mediated ion channels[14].

5.VIGABATRIN:- Vigabatrin (VGB) is a drug closely resembling gamma-aminobutyric acid (GABA), a neurotransmitter. By inhibiting the breakdown of GABA, VGB elevates its levels in the brain, thereby curbing neuronal hyperactivity, which underlies its antiepileptic effect. As a first-line treatment, VGB is particularly effective in managing infantile spasms, especially in patients with tuberous sclerosis complex. Its efficacy in addressing focal seizures is comparable to that of primary antiepileptic drugs such as carbamazepine, with similar side effects. However, the main drawback of VGB usage lies in the significant risk of irreversible visual field loss, a concern exacerbated by high doses, prolonged exposure, and increasing patient age[15].

6.VALPROIC ACID:- Valproic acid (VPA), also referred to as valproate, is one

of the most frequently prescribed medications for epilepsy treatment. It is estimated that around one million individuals worldwide use VPA on a daily basis. The mechanism of action of VPA involves enhancing the effects of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) through several means: inhibiting GABA degradation, suppressing GABA transamination activity, and stimulating GABA synthesis. Moreover, VPA prolongs N-methyl-D-aspartate-mediated stimulation while also inhibiting calcium and sodium channels.

Valproic acid (VPA) suppresses histone deacetylases (HDACs), promoting histone acetylation and loosening chromatin structure. This process facilitates gene expression and offers favorable effects for conditions such as cardiac arrhythmia, cardiac fibrosis, cardiac hypertrophy, hypertension, and myocardial infarction[16].

7.FELBAMATE:- Felbamate, known as FBM, is highly effective in treating focal seizures and Lennox-Gastaut syndrome. FDA approved it in 1993 specifically for partial epilepsy treatment, often used alone or alongside CBZ and PHT for uncontrolled focal epilepsy. Chemically, FBM is 2-phenyl-1,3-propanediol dicarbamate. Initially synthesized in the late 1950s to study the structure-activity relationship of the widely used anxiolytic drug meprobamate[19].

ADVERSE EFFECTS OF ANTICONVULSANTS:-

1.Certain antiseizure drugs (ASDs) have the potential to induce central nervous system deterioration, neuronal demise, aplastic anemia, liver failure, and in severe cases, fatalities such as sudden unexpected death in epilepsy (SUDEP)[17].

2.Carbamazepine has the potential to induce neural tube defects and craniofacial abnormalities[10].

3.The utilization of phenytoin is linked to fetal hydantoin syndrome[10].

4.Topiramate administration in the initial trimester of pregnancy is correlated with a tenfold rise in the risk of oral clefts. Phenobarbital usage can lead to congenital malformations, primarily cardiac defects.[10].

5.Phenobarbital induces a spectrum of adverse effects, spanning from renal failure, myocardial dysfunction, and sedation, to respiratory depression, contingent on the dosage. These effects may encompass diminished consciousness levels, hypotension, paralysis, and coma, particularly at high doses or due to drug accumulation attributed to its extended half-life of 3-7 days[11].

6.Carbamazepine and phenytoin were identified as the medications most closely linked to reductions in T4 and T3 hormone levels, whereas topiramate notably increased TSH levels. Oxcarbazepine has been associated with decreased levels of serum FT4 and FT3, indicating potential central hypothyroidism. Phenobarbital demonstrated a significant reduction in FT3 levels. Levetiracetam and valproic acid use may lead to subclinical hypothyroidism. Lamotrigine was observed to have the least impact on thyroid hormone levels among the antiseizure drugs studied[18].

19.Recently, there has been increased attention on additional side effects including:

1.Weight alterations.

2. Blocking carbonic anhydrase, potentially resulting in metabolic acidosis, kidney stone formation, reduced sweating, and intolerance to heat

3.Stimulating enzyme activity

4. Adverse effects on vision.

5. Negative reactions on the skin.

6. Other adverse effects such as liver toxicity, kidney damage, colitis, and the

onset of systemic lupus erythematosus (SLE).[20].

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